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ASSOCIATION OF URINARY MELATONIN LEVELS AND AGING-RELATED OUTCOMES IN OLDER MEN

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Abstract

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Background—Circadian disruptions can contribute to accelerated aging, and the circadian system regulates cognitive and physical functions; therefore, circadian markers (e.g., melatonin) may be associated with key aspects of healthy aging and longevity.

Objective—To evaluate urinary melatonin levels in relation to cognitive function, physical function, and mortality among 2,821 older men in the Osteoporotic Fractures in Men Study

Design—Cohort study

Measurements—In 2003–2005, participants provided first-morning spot urine samples, which were assayed for 6-sulfatoxymelatonin (the primary melatonin metabolite in urine); cognitive and physical function assessments were completed twice, at baseline and an average of 6.5 years later. Participant deaths were confirmed by central review of death certificates over a mean of 9.2 years of follow up.

Results—In multivariable-adjusted regression models, we observed a significant trend of better Digit Vigilance Test scores (i.e., decreased time to completion) at baseline across increasing melatonin quartiles (p-trend=0.01); however, mean time-to-completion scores did not significantly differ comparing extreme quartiles (group means: 547.1 seconds (95% CI: 533.6, 560.6) versus 561.3 seconds (95% CI: 547.8, 574.9)), and there were no associations of urinary melatonin levels with other cognitive test scores, or any cognitive change scores over time. Furthermore, melatonin levels were not related to physical function scores (p-trends=0.4 for walking speed, 0.7 for chair stands, and 0.6 for grip strength in fully-adjusted models) or mortality risk (p-trend=0.3 in the fully-adjusted model).

Conclusion—We found little evidence of associations between urinary melatonin levels and key measures of healthy aging and mortality in this cohort of older men. Further research should explore the relation of melatonin, particularly if assessed earlier in life, and other circadian markers with healthy aging outcomes.

Keywords

Melatonin; cognitive function; physical function; mortality; aging

INTRODUCTION

The circadian system plays a fundamental role in regulating 24-hour cycles of physiologic function in humans, including the sleep/wake cycle, body temperature, metabolism, and blood pressure[1]. Epidemiologic studies have linked markers of circadian disruption (e.g., shift work, extreme/disturbed sleeping patterns, weaker circadian activity rhythms) with adverse health outcomes, including obesity[2, 3], type 2 diabetes[4, 5], cardiovascular disease[6–8], dementia[9], and mortality[10–13]. Because circadian disturbances have been implicated in accelerated aging[14], they have implications for overall health and function in older adults. There is growing appreciation for the critical role of the circadian system in regulating cognitive and physical functions, involving a well-coordinated system of biologic clocks: the master clock located in the suprachiasmatic nucleus of the brain, and many local clocks throughout the brain, peripheral organs, and skeletal muscles[15, 16]. Thus, circadian

rhythms may provide information about these key functional domains associated with healthy aging.

Melatonin, an idoleamine hormone produced by the pineal gland and entrained to the environmental light/dark cycle, is the primary molecular marker of the circadian system. It is involved in important signaling pathways at the cellular level, and is thought to have anti-oxidant and anti-inflammatory properties[17]—observations supporting the notion that melatonin might play a role in health promotion and disease prevention for older adults[18]. In humans, research has focused primarily on melatonin supplementation and/or bright light therapy and cognitive function in patients with existing cognitive impairment[19–27]; however, research is extremely limited on the association of endogenous melatonin levels (a key marker of circadian rhythms) with important aspects of healthy aging [28, 29]. Thus, we evaluated urinary melatonin levels in relation to cognitive function, physical function, and mortality in older, community-dwelling men participating in the Osteoporotic Fractures in Men (MrOS) Study.

METHODS

Study population

The MrOS study is a multi-center study, initially designed to examine risk factors for bone fracture among 5,994 older men. Participants were aged 65 years or older, were community-dwelling, and were enrolled at one of six study centers located across the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; the Monogahela Valley near Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California[30, 31]. Men were excluded from the study if they required walking assistance, or previously had a bilateral hip replacement. All participants gave written informed consent for the study, and the institutional review board of each study center approved the study protocol.

From December 2003 through March 2005, 3,135 participants completed an ancillary sleep study; the remainder of participants chose not to participate in the sleep study (n=1,997), died prior to initiation of the sleep study (n=349), had previously terminated their participation in the overall study (n=40), were not eligible for the sleep study (n=150), or were not invited to participate in the sleep study because recruitment goals already had been achieved (n=323). As part of the sleep study, men provided first-morning spot urine samples, and 2,883 participants had their samples assayed for melatonin; 39 samples were not used because their results were off the standard curve, and 23 samples were excluded because these men were taking melatonin supplements, leaving 2,821 eligible participants whose melatonin levels were assessed (Figure 1).

In addition, participants in the sleep study underwent cognitive and physical function testing twice, at baseline and an average of 6.5 years later. Participant deaths were tracked by death certificates throughout follow up of the study.

Urine collection and melatonin measurements

Participants collected first-morning urine samples in their homes, with instructions and supplies provided at the time of participation in the ancillary sleep study. These samples

were stored in participants' refrigerators until retrieval by a member of the research staff, at which point they were processed and stored (at −80 degrees Celsius) for up to two weeks at the participant's clinic site. Subsequently, urine samples were sent to a central repository (Biomedical Research Institute, Rockville, Maryland) and archived in liquid nitrogen at −190 degrees Celsius. Melatonin assays were conducted at the Oregon Health and Science University, Oregon Clinical and Translational Research Institute Core Laboratory, using the Bühlmann enzyme-linked immunosorbent assay (ALPCO Diagnostics, Windham, New Hampshire) to measure the concentration of 6-sulfatoxymelatonin—the major urinary metabolite of melatonin. Assays were performed in duplicate and averaged, and were repeated when results did not coincide with the standard curve or when duplicate measurements were not similar; 16% of samples were repeated. 6-sulfatoxymelatonin measurements were creatinine standardized to account for differences in urine concentration; creatinine was measured at the Portland Veterans Administration Hospital clinical laboratory using a Roche COBAS Integra 6000 automated analyzer (Roche Diagnostics Corporation, Indianapolis, Indiana). For quality control, two samples with known 6-sulfatoxymelatonin concentrations and a pooled urine sample from 120 anonymous donors were included with each assay run. The mean value of 6-sulfatoxymelatonin measured in the pooled sample was 7.97 ng/mL (standard deviation=1.12 ng/mL) before creatinine standardization; based on this sample, inter- and intra- assay coefficients of variation were 12.5% and 5.0%, respectively.

Although use of a single 6-sulfatoxymelatonin measurement is subject to intra-individual variability, first-morning urine measurements have been shown to remain fairly stable when measured repeatedly over time[32, 33].

Cognitive function assessment

Participants completed three cognitive tests: the Modified Mini-Mental State Examination (3MS), the Trail Making Test Part B (Trails B), and the Digit Vigilance Test (DVT). The 3MS is a test of global cognitive function, including orientation, concentration, language, praxis, and memory[34]. Scores range from 0 to 100, with higher scores indicating better cognitive function. Trails B is a test of executive function, which evaluates aspects of attention, concentration, psychomotor speed, cognitive shifting, and complex sequencing function[35, 36]. It requires participants to connect numbers and letters in a particular sequence, while shifting between sets of numbers and letters; a faster time to completion (in seconds) indicates better cognitive function. DVT is a vigilance test that requires participants to cross out all of the number 6's that appear in 59 rows of 35 digits[37]. In this cohort, the test was modified to increase difficulty by instructing participants to cross out 6's only if they were followed by a higher number (i.e., 7, 8, or 9).

Physical function assessment

Several aspects of physical function were evaluated, including gait speed, chair stand ability, and grip strength. To assess gait speed, participants were instructed to walk a six-meter standard course at their normal walking pace, and their time to completion was recorded in seconds; walking speed was calculated in meters/second. To measure chair stand ability, men were asked to rise from a standard chair without using their arms, and time needed to

complete five chair stands was recorded. Participants were considered unable to perform chair stands if they refused to rise, were unable to stand without using their arms, or needed assistance from another person; these men were excluded from our analyses. To assess grip strength, participants were instructed to squeeze a Jamar dynamometer as hard as they could, and the average of four trials (two on each hand) was calculated in kilograms; all participants used the same type of dynamometer and followed same procedures.

Death ascertainment

Once participants were enrolled in the cohort, they were contacted by mail or telephone every four months through February 2016; a participant's next of kin was contacted if the participant could not be reached. When a participant death was reported, a central study physician determined the date and cause of death using a pre-specified adjudication protocol and information from death certificates and medical records.

Other measures

Participants reported information about demographics, medical history, health and functional status, dietary habits, and lifestyle factors on questionnaires administered at the time of the ancillary sleep study. The Physical Activity Scale for the Elderly was used to estimate participants' activity levels[38], and the Geriatric Depression Scale was used to assess whether participants had depressive symptoms[39]. The Short Form 12-item health survey was used to evaluate general health, and participants were asked to rate their self-perceived health as well[40]. Body-mass index (in kg/m^2) and bone mineral density (in g/cm^2), using dual x-ray absorptiometry scans, were measured during the clinical examination of sleep study participants; serum samples were also collected at this time, and subsequently assayed for 25-hydroxyvitamin D levels (a marker of vitamin D status). Use of prescription and non-prescription medication was determined when participants brought their current medications to the study clinic, where they were entered into an electronic database and each medication was matched to its ingredient(s) based on the Iowa Drug Information Service (IDIS) Drug Vocabulary (College of Pharmacy, University of Iowa, Iowa City, IA)[41].

Statistical analysis

The baseline characteristics of our participants were evaluated across quartiles of urinary melatonin levels, using means and standard deviations for continuous variables and percentages for categorical variables. P-values were obtained for these comparisons using analysis of variance for normally-distributed continuous data, the Kruskal-Wallis test for skewed continuous data, and chi-squared tests for categorical data.

For analyses of cognitive and physical function, we used multivariable-adjusted linear regression to estimate mean differences (with 95% confidence intervals (CI)) in baseline scores and change scores over time, across quartiles of creatinine-adjusted urinary melatonin levels (approximated by 6-sulfatoxymelatonin, a major urine metabolite of melatonin). In addition, we used multivariable-adjusted Cox proportional hazard regression to estimate relative risks (RR) of mortality over follow up across quartiles of urinary melatonin. Proportional hazard assumptions were evaluated by visually checking log-minus-log plots and Schoenfeld residual plots versus survival time for the association between urinary

melatonin and mortality; there was no evidence of violation. For all analyses, initial models were adjusted for age and clinic site only, and additional confounding variables were included based on a backward elimination procedure; specifically, we considered the covariates listed in Table 1, and retained variables in a stepwise fashion with $p<0.1$. Backward elimination was performed separately for models of cognitive function, physical function, and mortality; therefore, final models for each of these outcomes included different sets of covariates. For all models, p-trends were calculated based on the adjusted least-square mean values associated with each quartile of urinary melatonin.

In sensitivity analyses, we re-evaluated associations of urinary melatonin with cognitive and physical function scores that were transformed when outcome distributions were skewed. We also examined all associations of interest while excluding users of beta blockers because these medications can decrease melatonin levels[42].

All significance levels were two sided and $p<0.05$ was considered significant. Analyses were conducted using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Participant characteristics

We observed modest differences in baseline characteristics of the study population across quartiles of urinary melatonin levels (Table 1). There was a slight decrease in mean age and body-mass index, and slight increase in physical activity, across increasing quartiles of melatonin. In addition, the percentage of men with hypertension, congestive heart failure, myocardial infarction, diabetes, and beta blocker use was lower with increasing quartiles of melatonin; in contrast, use of calcium supplements was greater over these quartiles.

Association of urinary melatonin levels and cognitive function

We found that baseline cognitive function scores were similar across quartiles of urinary melatonin levels for the 3MS and Trails B tests, both in models adjusted for age and clinic site and models adjusted for additional covariates (Table 2). For the DVT, there was a trend toward better scores (i.e., decreased time to completion) with increasing melatonin levels (p-trend=0.01 in the fully-adjusted model); however, mean DVT scores did not decrease consistently over increasing melatonin quartiles. Furthermore, we observed no associations between melatonin levels and change in cognitive scores over a mean follow-up time of 6.5 years (e.g., p-trends for fully-adjusted models were 0.6 for the 3MS, 0.1 for the Trails B, and 0.2 for the DVT) (results not shown in tables).

Association of urinary melatonin levels and physical function

We observed slightly higher mean gait speeds over increasing quartiles of urinary melatonin levels in age- and clinic- adjusted models (p-trend=0.03), with average speed rising incrementally from 1.13 (95% CI: 1.11, 1.14) in the lowest quartile to 1.15 (95% CI: 1.13, 1.16) in the highest quartile of melatonin (Table 3). However, when additional covariates were included in final model, this trend was attenuated and became non-significant (p-trend in fully-adjusted model=0.4). In addition, there was no association of urinary melatonin and

either time to complete chair stands or grip strength (e.g., p-trends=0.7 and 0.6, respectively, in the fully-adjusted model), and melatonin levels were not related to change in gait speed, chair stands, and grip strength over an average of 6.5 years of follow up (e.g., p-trends from fully-adjusted models=0.8, 0.9, and 0.06, respectively).

Association of urinary melatonin levels and mortality

Mean follow-up time to death was 9.2 years in this cohort. There was a modest association between urinary melatonin levels and overall mortality in our minimally-adjusted model (p-trend=0.03), although this association was attenuated and became non-significant in the fully-adjusted model (p-trend=0.3). Furthermore, the fully-adjusted relative risk for overall mortality was non-significant comparing extreme quartiles of urinary melatonin (RR: 1.13, 95% CI: 0.94, 1.36). When we evaluated cardiovascular disease-related mortality, there was no association between urinary melatonin levels and morality risk in either the minimally-adjusted model (p-trend=0.1) or the model fully adjusted for potential confounding factors (p-trend=0.3). The relative risk of cardiovascular disease-related mortality was also non-significant comparing extreme quartiles of urinary melatonin levels (e.g., RR: 1.20, 95% CI: 0.89, 1.61 with full adjustment for covariates).

Sensitivity analyses

In sensitivity analyses, results were similar when we examined the association of urinary melatonin levels with transformed cognitive and physical function scores, and when we excluded beta blocker users from our analyses (results not shown).

DISCUSSION

Overall, we found little association of urinary spot collections of melatonin levels with key aging-related functional domains and mortality in this cohort. In particular, melatonin levels did not vary according to baseline cognitive scores (on two of three tests) or baseline physical function scores, change scores over time for either cognitive or physical function, or mortality risk. We did observe a significant trend between melatonin levels and DVT scores, indicating better DVT scores over increasing quartiles of urinary melatonin; however, qualitatively, this trend was based on an inconsistent pattern of DVT scores. Thus, our findings do not indicate that melatonin levels derived from first-morning urine samples predict key indicators of healthy aging and longevity.

A previous study of urinary melatonin levels and cognitive function was conducted in the HEIJO-KYO cohort, a community-based study of 1,105 older adults in Japan[28]. In this cross-sectional study, participants provided urine samples comprised of total volume voided in one night and then completed the Mini-Mental State Examination (MMSE); results suggested a weak association between higher levels of urinary melatonin and decreasing odds of cognitive impairment (defined as MMSE ≤26 points; p-trend=0.048). For example, cognitive impairment was 30% less likely (95% CI: 0.46, 1.06) among participants in the highest versus lowest quartile of melatonin; however, this odds ratio was not statistically significant. Moreover, while these results were adjusted for demographic, lifestyle, and circadian parameters (e.g., duration in bed, night-time light levels), additional adjustment for

alcohol intake, depressed mood, and health conditions was undertaken piecemeal in separate models, all with borderline significant trends. Thus, full adjustment for covariates in one model might attenuate these trends and render them statistically non-significant. In addition, several studies have examined the cognitive effects of melatonin supplementation in patients with existing cognitive impairment or Alzheimer's disease[19–27]. However, a Cochrane systematic review[43] and a recent meta-analysis[44] found insufficient evidence from randomized trials to conclude that melatonin supplementation could improve cognitive impairment in dementia patients. Thus, existing research on melatonin and cognition in older adults is generally consistent with the null findings that we report in our study, including longitudinal analyses of cognitive decline over time.

Prior studies examining melatonin in relation to physical function are more limited, and no existing studies have evaluated melatonin and mortality in humans. In the HEIJO-KYO cohort, a small cross-sectional study found that higher urinary melatonin levels were associated with increased grip strength among 355 older men (p-trend=0.002, multivariable-adjusted mean differences: 32.4, 33.3, 34.9, and 35.2 kg across increasing quartiles of melatonin), as well as increased quadriceps strength in these men (p-trend=0.02, adjusted mean differences: 186.9, 217.5, 210.7, and 221.7 Nm across increasing quartiles of melatonin). This result appears to contrast with the null association between urinary melatonin and grip strength that we identified in the present study, which might be attributable to the exclusion of men with greater functional limitations in MrOS (i.e., those who needed walking assistance or had undergone bilateral hip replacement). While these exclusions could limit the generalizability of our findings to individuals with greater functional capacity, they also reduce the potential influence of confounding by underlying health status or frailty, which may be otherwise difficult to fully control using multivariable modeling. It is therefore possible that results from the elderly HEIJO-KYO cohort might be explained by such residual confounding. Furthermore, we provide additional data suggesting that urinary melatonin is not associated with physical function decline based on repeated measures of grip strength over time. Clearly, more research is necessary to explore associations of urinary melatonin levels, physical function, and mortality in older adults.

Still, initial research indicates that circadian activity rhythms over the 24-hour day may predict aging outcomes in older adults. In the Study of Osteoporotic Fractures, activity patterns were monitored with wrist actigraphy over three 24-hour periods among 1,287 community-dwelling older women, and temporal patterns indicating weaker circadian activity rhythms (i.e., lower amplitude and mesor, and later acrophase) were related to poorer cognitive function[45] and higher incidence of mild cognitive impairment and dementia[9] five years later. Similar findings have been reported in the same cohort related to mortality, suggesting that decreased activity rhythms may be associated with greater risk of death in older women[12]. Although similar research has not been conducted in men to date, these findings suggest that systems-level circadian parameters may provide further information about key aging outcomes in older adults. Future studies also should explore circadian activity rhythms in relation to physical function at older ages, as well as other system-level parameters with aging outcomes.

Limitations of our study should be considered. First, we used first-morning spot urine samples to assess melatonin at only one time point. Creatinine-standardized 6-sulfatoxymelatonin measurements from first-morning urine samples are considered reliable for estimating overnight melatonin production[46, 47], and were highly correlated with creatinine-standardized 6-sulfatoxymelatonin levels obtained from 24-hour urine specimens in this cohort (ρ=0.83, $p<0.0001$, unpublished results). However, our urine samples were collected when participants were already older in age and therefore melatonin levels were relatively low; for example, mean 6-sulfatoxymelatonin levels were 10.75 ng/mg creatinine in this study, compared to 29.7 ng/mg creatinine in a sample of young to middle-aged day-working men[48]. Furthermore, timing of melatonin secretion is known to be a strong marker of the circadian system[49], and such a measurement was unavailable in our cohort; thus, we cannot rule out the possibility of an association between this specific measurement and aging outcomes evaluated in our study. Second, our cognitive battery was limited to tests of global cognitive function (i.e., 3MS) and executive function (i.e., Trails B and DVT), but not other cognitive domains (e.g., memory); still, many important associations have been identified with these cognitive measures in the MrOS cohort[50, 51]. Nonetheless, we could have missed associations between melatonin and cognitive function if they were specific to other cognitive domains. Finally, we studied a group of generally healthy, community-dwelling, mostly Caucasian men, and therefore our results may not be generalizable to other populations, including women. Our evaluation of physical function in a cohort excluding participants with certain functional limitations (e.g., need for assistance while walking) may also have limited interpretation to healthier older populations.

In summary, these results do not suggest that first-morning urinary melatonin levels, if measured later in life at a single time point, are related to cognitive and physical function and decline, as well as mortality, in older men. More studies are needed to address these associations in older men and women, and to explore additional circadian markers in relation to healthy aging.

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Highlights

- Urinary melatonin levels, measured at a single point in later life, were not associated with cognitive or physical function in this cohort of older men.
- These melatonin levels also were not related to mortality, including cardiovascular-related mortality, in this cohort.
- Further research should explore melatonin levels, particularly if assessed earlier in life, and other circadian markers with health aging outcomes in older men and women.

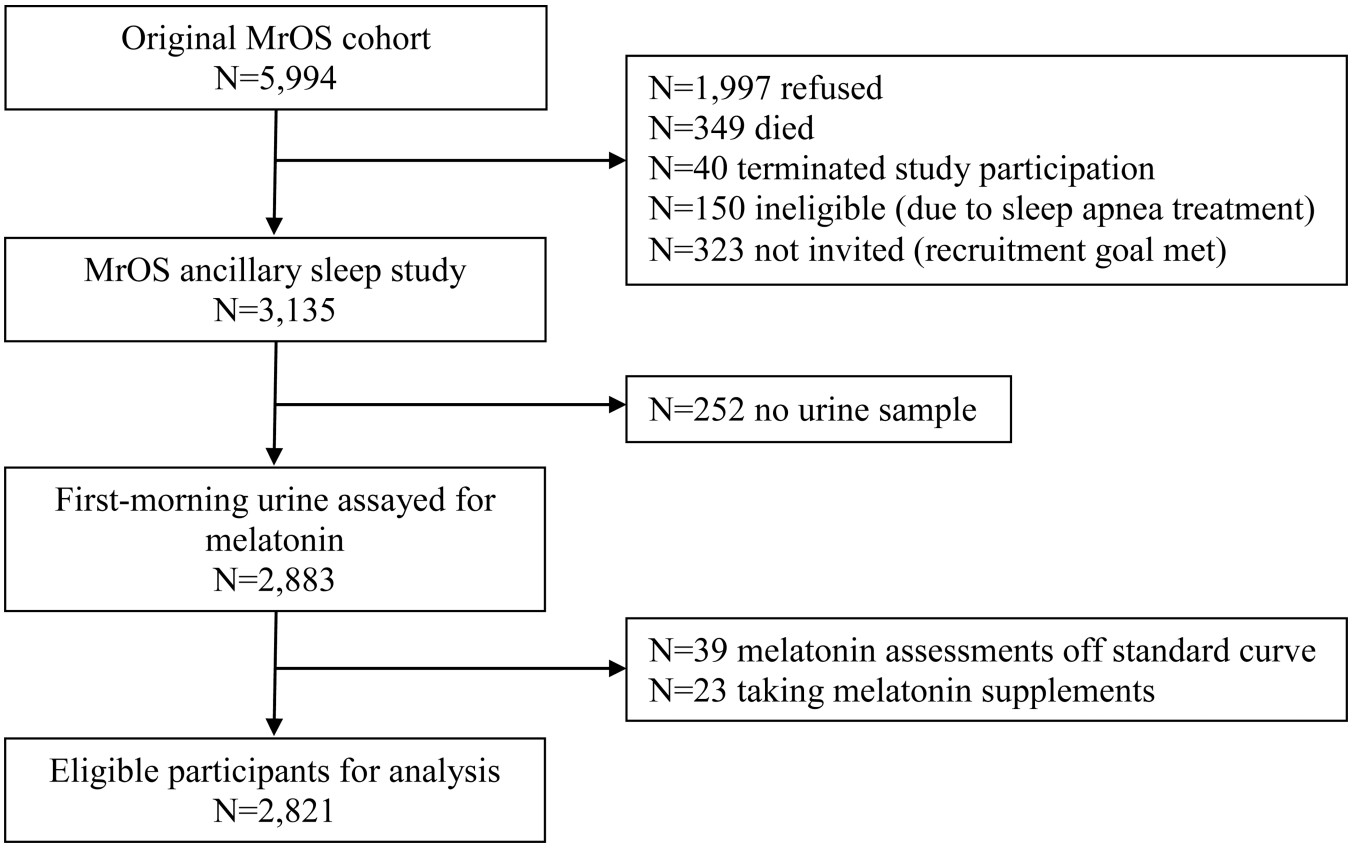

Figure 1.
Flow Chart of MrOS Participants Included in Analyses of Urinary Melatonin and Cognitive Function, Physical Function, and Mortality

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Table 1

Baseline Characteristics of 2,821 Participants in the Osteoporotic Fractures in Men Study (United States, 2003–2005), Across Quartiles of Urinary Melatonin Levels

	Urinary melatonin levels				
	Quartile 1, <4.45 ng/mg creatinine	**Quartile 2, 4.45–8.39 ng/mg creatinine**	**Quartile 3, 8.40–14.18 ng/mg creatinine**	**Quartile 4, >14.19 ng/mg creatinine**	**p-trend**
Age, years, mean (SD)	76.7 (5.7)	76.5 (5.7)	76.5 (5.5)	75.7 (5.4)	0.0004
Caucasian, %	89.7	94.0	91.2	92.8	0.15
Education, %					
High school or less	5.8	4.5	6.5	4.7	0.25
Some college or college degree	17.3	16.3	17.2	14.4	
Graduate school	76.9	79.2	76.3	80.9	
Body-mass index, kg/m^2, mean (SD)	27.4 (3.8)	27.5 (3.8)	27.0 (3.7)	26.7 (3.8)	0.0001
Physical Activity Scale for the Elderly, mean (SD)	142.6 (71.6)	138.0 (68.2)	151.4 (74.1)	149.2 (69.3)	0.005
Geriatric Depression Scale >6, %	7.1	7.0	5.7	6.4	0.41
Antidepressant use, %	8.1	9.7	6.5	7.1	0.18
Current smoker, %	1.8	2.1	2.3	1.8	0.95
Alcohol intake, %					
None	36.2	35.1	33.9	31.9	0.15
1–13 drinks per week	57.7	59.7	61.4	62.0	
>13 drinks per week	6.1	5.2	4.7	6.1	
Short Form 12-item health survey score, mean (SD)	47.6 (10.7)	48.4 (9.9)	49.8 (9.7)	48.7 (10.2)	0.008
Self-reported health (excellent or good), %	85.5	86.1	88.5	87.1	0.22
Independent activities of daily living, at least one impairment, %	23.1	22.3	16.5	21.0	0.07

	Urinary melatonin levels				
	Quartile 1, <4.45 ng/mg creatinine	**Quartile 2, 4.45–8.39 ng/mg creatinine**	**Quartile 3, 8.40–14.18 ng/mg creatinine**	**Quartile 4, >14.19 ng/mg creatinine**	**p-trend**
Total hip bone mineral density, g/cm^2, mean (SD)	0.96 (0.14)	0.97 (0.14)	0.96 (0.14)	0.94 (0.14)	0.006
Hypertension, %	54.2	50.9	47.7	45.7	0.0006
Congestive heart failure, %	9.1	6.2	4.7	4.4	0.0001
Myocardial infarction, %	21.0	17.7	15.3	14.9	0.001
Diabetes, %	15.7	13.3	12.2	11.2	0.01
Stroke, %	3.7	4.5	2.7	4.1	0.86
Parkinson’s disease, %	1.1	1.3	1.4	1.3	0.76
Sleep medication, %	10.8	10.8	11.6	10.3	0.93
Benzodiazepine, %	4.7	6.1	4.0	3.5	0.11
Non-benzodiazepine, %	2.1	1.0	2.7	2.3	0.37
Beta blockers, %	38.3	28.8	22.6	17.9	<0.0001
Vitamin D supplements, %	61.8	60.9	64.8	62.6	0.44
Calcium supplement use, %	26.5	30.6	31.8	34.3	0.002
Serum vitamin D levels, mean (SD)	28.1 (8.6)	29.0 (8.6)	29.0 (8.7)	29.3 (9.3)	0.01
Non-steroidal anti-inflammatory drug use, %	19.3	21.6	18.2	22.4	0.39

SD=standard deviation

Table 2

Means of Baseline Cognitive Function Scores, With 95% Confidence Intervals, Across Quartiles of Urinary Melatonin Levels in the Osteoporotic Fractures in Men Study (United States, 2003–2005)

	Urinary melatonin levels				
Cognitive function measures [a]	**Quartile 1, <4.45 ng/mg creatinine**	**Quartile 2, 4.45–8.39 ng/mg creatinine**	**Quartile 3, 8.40–14.18 ng/mg creatinine**	**Quartile 4, >14.19 ng/mg creatinine**	**p-trend**
3MS					
Model 1 [b] (n=2,818)	92.7 92.2, 93.1	92.5 92.1, 93.0	92.8 92.3, 93.2	92.8 92.4, 93.3	0.5
Model 2 [c] (n=2,730)	92.9 92.5, 93.3	92.6 92.2, 93.0	92.7 92.2, 93.1	92.9 92.4, 93.3	1.0
Trails B					
Model 1 [b] (n=2,729)	120.3 116.4, 124.2	125.2 121.4, 129.1	119.7 115.9, 123.5	119.1 115.3 123.0	0.3
Model 3 [d] (n=2,620)	117.8 114.0, 121.7	125.4 121.6, 129.3	119.5 115.7, 123.3	118.0 114.2, 121.8	0.5
DVT					
Model 1 [b] (n=2,748)	563.8 550.1, 577.4	574.0 560.3, 587.7	535.7 522.1, 549.3	549.7 536.1, 563.3	0.01
Model 4 [e] (n=2,714)	561.3 547.8, 574.9	574.5 560.9, 588.1	539.3 525.8, 552.7	547.1 533.6, 560.6	0.01

3MS=Modified Mini-Mental State Examination; DVT=Digit Vigilance Test; Trails B=Trail Making Test Part B

[a] For interpretation of these cognitive function tests, higher 3MS and DVT scores and lower Trails B scores indicate better cognitive function.

[b] Adjusted for age and clinic site.

[c] Adjusted for age, clinic site, calcium supplements, short Form 12-item health survey score, independent activities of daily living, and serum vitamin D level.

[d] Adjusted for age, clinic site, hypertension, calcium supplements, total hip bone mineral density, short Form 12-item health survey score, independent activities of daily living, and serum vitamin D level.

[e] Adjusted for age, clinic site, body-mass index, hypertension, total hip bone mineral density, short Form 12-item health survey score, and independent activities of daily living.

Table 3

Means of Baseline Physical Function Scores, With 95% Confidence Intervals, Across Quartiles of Urinary Melatonin Levels in the Osteoporotic Fractures in Men Study (United States, 2003–2005)

	Urinary melatonin levels				
Physical function measures [a]	**Quartile 1, <4.45 ng/mg creatinine**	**Quartile 2, 4.45–8.39 ng/mg creatinine**	**Quartile 3, 8.40–14.18 ng/mg creatinine**	**Quartile 4, >14.19 ng/mg creatinine**	**p-trend**
Walking speed					
Model 1 [b] (n=2,788)	1.13 1.11, 1.14	1.14 1.13, 1.16	1.15 1.14, 1.17	1.15 1.13, 1.16	0.03
Model 2 [c] (n=2,679)	1.14 1.12, 1.15	1.14 1.13, 1.16	1.14 1.13, 1.16	1.15 1.13, 1.16	0.4
Chair stands					
Model 1 [b] (n=2,643)	11.9 11.6, 12.1	11.7 11.5, 12.0	11.3 11.0, 11.6	11.8 11.5, 12.1	0.3
Model 3 [d] (n=2,539)	11.7 11.4, 12.0	11.7 11.4, 11.9	11.5 11.3, 11.8	11.8 11.6, 12.1	0.7
Grip strength					
Model 1 [b] (n=2,761)	37.8 37.2, 38.3	37.5 37.0, 38.1	38.0 37.5, 38.6	38.1 37.5, 38.6	0.3
Model 4 [e] (n=2,673)	38.0 37.5, 38.6	37.7 37.1, 38.2	37.8 37.3, 38.4	38.2 37.6, 38.7	0.6

[a] For interpretation of these physical function tests, higher walking speed and grip strength scores and lower chair stands scores indicate better physical function.

[b] Adjusted for age and clinic site.

[c] Adjusted for age, clinic site, body-mass index, physical activity scale for the elderly, congestive heart failure, hypertension, total hip bone mineral density, short form 12-item health survey score, independent activities of daily living, and serum vitamin D level.

[d] Adjusted for age, clinic site, body-mass index, physical activity scale for the elderly, congestive heart failure, myocardial infarction, total hip bone mineral density short form 12-item health survey score, independent activities of daily living, and serum vitamin D level.

[e] Adjusted for age, clinic site, body-mass index, physical activity scale for the elderly, congestive heart failure, hypertension, short form 12-item healthy survey score, independent activities of daily living, and serum vitamin D level.

Table 4

Relative Risk of Mortality, With 95% Confidence Intervals, Across Quartiles of Urinary Melatonin Levels in the Osteoporotic Fractures in Men Study (United States, 2003–2015)

	Urinary melatonin levels				
	Quartile 1, <4.45 ng/mg creatinine	**Quartile 2, 4.45–8.39 ng/mg creatinine**	**Quartile 3, 8.40–14.18 ng/mg creatinine**	**Quartile 4, >14.19 ng/mg creatinine**	**p-trend**
Overall mortality					
Model 1 [a] (n=2,664)	1.16 0.98, 1.37	1.07 0.90, 1.27	0.93 0.78, 1.11	1.00 (reference)	0.03
Model 2 [b] (n=2,284)	1.13 0.94, 1.36	0.99 0.82, 1.20	1.02 0.84, 1.24	1.00 (reference)	0.3
Cardiovascular disease-related mortality					
Model 1 [a] (n=1,947)	1.26 0.95, 1.67	1.00 0.74, 1.34	0.87 0.65, 1.17	1.00 (reference)	0.1
Model 2 [c] (n=1,845)	1.20 0.89, 1.61	0.88 0.64, 1.21	0.99 0.73, 1.36	1.00 (reference)	0.3

3MS=Modified Mini-Mental State Examination; DVT=Digit Vigilance Test; Trails B=Trail Making Test Part B

[a]Adjusted for age and clinic site.

[b]Adjusted for age, clinic site, hypertension, myocardial infarction, chair stands, serum vitamin D level, physical activity scale in the elderly, short form 12-item healthy survey score, Trails B score, 3MS score, DVT score, and grip strength.

[c]Adjusted for age, clinic site, hypertension, congestive heart failure, myocardial infarction, walking speed, serum vitamin D level, physical activity scale for the elderly, Trails B score, 3MS score, and DVT score.